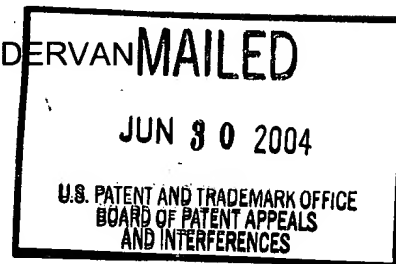


UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte ELDON E. BAIRD and PETER B. DERVAN

Appeal No. 2003-0395
Application No. 09/374,704



ON BRIEF

Before WILLIAM F. SMITH, SCHEINER and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of
claims 1, 3-19, 25 and 26. Claims 20-24, also pending, have been allowed.

Claims 1 and 8 are representative of the subject matter on appeal:

1. A polyamide molecule that specifically binds to base pairs in the minor groove
of a DNA molecule, said polyamide molecule comprising:

one or more amino acids comprising a moiety selected from the group consisting
of N-methylpyrrole, 3-hydroxy-N-methylpyrrole, and N-methylimidazole, wherein one or
more of said amino acid(s) are not α -amino acids; and

a positive patch consisting of a rigid group adjacent to a positively charged
group, said rigid group comprising a first and a second amino acid; said first amino acid
being selected from the group consisting of arginine, proline, lysine, and
hydroxyproline; said second amino acid being selected from the group consisting of
proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, and
hydroxyproline.

8. The polyamide of claim 1 wherein the positive patch comprises the amino
acid sequence Arg-Pro-Arg.

The references relied on by the examiner are:

Feng et al. (Feng), "Hin Recombinase Bound to DNA: The Origin of Specificity in Major and Minor Groove Interactions," Science, Vol. 263, pp. 348-355 (January 21, 1994)

Parks et al. (Parks), "Recognition of 5'-(A,T)GG(A,T)₂-3' Sequences in the Minor Groove of DNA by Hairpin Polyamides," J. Am. Chem. Soc., Vol 118, pp. 6153-6159 (1996)

Trauger et al. (Trauger), "Extension of Sequence-Specific Recognition in the Minor Groove of DNA by Pyrrole-imidazole Polyamides to 9-13 Base Pairs," J. Am. Chem. Soc., Vol 118, pp. 6160-6166 (1996)

Swalley at al. (Swalley), "Recognition of a 5'-(A,T)GGG(A,T)₂-3' Sequence in the Minor Groove of DNA by an Eight-Ring Hairpin Polyamide," J. Am. Chem. Soc., Vol 118, pp. 8198-8206 (1996)

Claims 1, 3-19, 25 and 26 stand rejected under 35 U.S.C. § 103 as unpatentable over Swalley, Parks, Trauger and Feng.

We reverse.

BACKGROUND

"Several approaches for the development of synthetic ligands which interfere with protein-DNA recognition have been reported" (Specification, page 2). Polyamides have been found . . . to inhibit transcription factor binding and expression of a designated gene" (id.) "in cases where contacts in the minor groove are important for protein-DNA binding affinity" (id., page 3). "Polyamides containing *N*-methylpyrrole (Py) and *N*-methylimidazole (Im) amino acids bind to predetermined sequences in the minor groove of DNA with affinities and specificities comparable to naturally occurring DNA binding proteins . . . Sequence specificity is determined by a code of oriented side-by-side pairings of the Py and Im amino [acids] . . . An Im/Py pairing targets a G•C base

pair, while [a] Py/Im pair recognizes C•G. The Py/Py pair is degenerate and targets both A•T and T•A base pairs" (id., pages 1-2), thus, "Py/Im polyamides offer a potentially general approach for gene regulation, provided that efficient inhibition of DNA-binding can be achieved for a variety of transcription factors" (id., pages 1-2).

The present "invention relates to polyamides which bind to pre-determined sites of the minor groove of double-stranded DNA and have an α -amino acid domain ("positive patch") capable of inhibiting the activity of major groove DNA-binding proteins" (id., page 1). "[T]he positive patch comprises a rigid group joined to a positively charged group. The rigid group positions the positively charged group such that" (id., page 17) "[the] positive patch [], upon binding of the polyamide to the minor groove of a DNA molecule, is able to contact nucleotides in the major groove of [the] DNA molecule . . . alter[ing] the conformation of [the] DNA molecule such that the function of a conformation-dependent DNA binding protein is inhibited" (id., page 6).

DISCUSSION

Claim 1 is directed to a polyamide molecule comprising (1) one or more amino acids selected from the group consisting of *N*-methylpyrrole, 3-hydroxy-*N*-methylpyrrole and *N*-methylimidazole; and (2) a "positive patch consisting of a rigid group adjacent to a positively charged group," wherein the rigid group comprises a first amino acid (arginine, proline, lysine or hydroxyproline) and a second amino acid (proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine or hydroxyproline). Claim 8 specifies that the positive patch comprises the amino acid sequence Arg-Pro-Arg.

Swalley, Parks and Trauger describe various synthetic polyamides, containing *N*-methylpyrrole (Py) and *N*-methylimidazole residues in defined sequences, which recognize specific minor groove DNA sequences. None of the synthetic polyamides includes the “positive patch consisting of a rigid group adjacent to a positively charged group” required by the claims on appeal.

Feng describes the structure of the 52-amino acid DNA-binding domain of the prokaryotic Hin recombinase, which binds to the *hixL* and *hixR* sites on the Salmonella chromosome, catalyzing a site-specific DNA recombination reaction. The binding domain of Hin “consists of a compact bundle of three α -helices, with [an] extended amino-terminal arm and [a] carboxyl-terminal tail. α -Helix 1 [] lies parallel to the axis of the DNA, α -helix 2 [] is nearly antiparallel to helix 1 . . . and α -helix 3 [] is inserted in the major DNA groove parallel to the base pairs . . . The HTH [helix-turn-helix] motif formed by helices 2 and 3 is similar to those found in other prokaryotic regulatory DNA-binding proteins” (page 350, left-hand column). According to Feng, “ α -helix 3 is the DNA recognition helix for the Hin protein” (id.), but the six carboxy-terminal amino acids (Ile¹⁸⁵-Lys¹⁸⁶-Lys¹⁸⁷-Arg¹⁸⁸-Met¹⁸⁹-Asn¹⁹⁰) also interact with the minor groove of *hixL* and *hixR* (pages 351-352); as do four residues on the amino terminal arm (Gly¹³⁹-Arg¹⁴⁰-Pro¹⁴¹-Arg¹⁴²) (page 351). Among other things, Feng notes that “contacts made by the amino-terminal arm of the Hin DNA-binding domain are at least as critical to DNA recognition as those of helix 3” since “merely deleting Gly¹³⁹ and Arg¹⁴⁰ from the Hin DNA-binding peptide is sufficient to abolish specificity of binding to *hixL*” (page 351). As Feng summarizes it, “the recognition element of the [*hixL* and *hixR* sites] appears to involve two A•T base pairs [] recognized by amino acid residues Gly¹³⁹ and Arg¹⁴⁰ in the

minor groove, two non-specific base pairs [], and then a five base sequence [] recognized by helix 3 and the carboxyl-terminal tail in major and minor grooves, respectively" (page 354, center column).

According to the examiner, it would have been obvious to modify the polyamides described by Swalley, Parks and Trauger "with a sequence comprising Arg-Pro-Arg, since polyamide compounds comprising these sequence[s] were known to bind DNA with high affinity in a sequence specific manner[,] [t]hus providing additional polyamide compounds for DNA recognition" (Answer, page 5).

Nevertheless, we agree with appellants that the examiner's interpretation of Feng is overly simplistic, and that Feng, considered in its entirety, provides no motivation "to select the Arg-Pro-Arg sequence from a much larger protein structure, in order to graft the sequence onto a pyrrole- and imidazole-based polyamide" (Reply Brief, page 5). As appellants point out, it is the Hin recombinase's "helix-turn-helix motif [that] serves to present the Gly¹³⁹-Arg¹⁴⁰-Pro¹⁴¹-Arg¹⁴² sequence in precisely the proper orientation to interact with the DNA molecule" (id., page 6), and "[n]othing in [Feng] would indicate . . . that, in the absence of this helix-turn-helix motif, the 'Arg-Pro-Arg' sequence would exhibit any DNA binding properties whatsoever" (id., page 7). Moreover, "nothing of record indicates that this helix-turn-helix motif would exist in the pyrrole- and imidazole-based polyamides of [] Swalley, Parks, and Trauger" (id.).

At best, the examiner has established that individual elements of the claimed invention were known in the prior art. However, as explained in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. [] Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." []

Most if not all inventions arise from a combination of old elements. [] Thus, every element of a claimed invention may often be found in the prior art. [] However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. [] Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The examiner may establish a case of prima facie obviousness based on a combination of references "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." Id., 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

The rejection of claims 1, 3-19, 25 and 26 under 35 U.S.C. § 103 is reversed.

William F. Smith
Administrative Patent Judge

Toni R. Scheiner) BOARD OF PATENT
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Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES


Eric Grimes
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